Assessment of lexical semantic judgment abilities in alcohol-dependent subjects: An fMRI study

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Neuropsychological studies have shown that alcohol dependence is associated with neurocognitive deficits in tasks requiring memory, perceptual motor skills, abstraction and problem solving, whereas language skills are relatively spared in alcoholics despite structural abnormalities in the language-related brain regions. To investigate the preserved mechanisms of language processing in alcohol-dependents, functional brain imaging was undertaken in healthy controls (n=18) and alcohol-dependents (n=16) while completing a lexical semantic judgment task in a 3 T MR scanner. Behavioural data indicated that alcohol-dependents took more time than controls for performing the task but there was no significant difference in their response accuracy. fMRI data analysis revealed that while performing the task, the alcoholics showed enhanced activations in left supramarginal gyrus, precuneus bilaterally, left angular gyrus, and left middle temporal gyrus as compared to control subjects. The extensive activations observed in alcoholics as compared to controls suggest that alcoholics recruit additional brain areas to meet the behavioural demands for equivalent task performance. The results are consistent with previous fMRI studies suggesting compensatory mechanisms for the execution of task for showing an equivalent performance or decreased neural efficiency of relevant brain networks. However, on direct comparison of the two groups, the results did not survive correction for multiple comparisons; therefore, the present findings need further exploration.

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1. Introduction

There is considerable evidence that alcohol neurotoxicity from chronic alcohol consumption results in impaired performance in a variety of higher-order cognitive functions along with brain atrophy and altered regional brain metabolism (Parsons 1998; Sullivan *et al.* 2000; Oscar-Berman and Marinkovic 2003; Crews and Nixon 2009). Studies have shown that alcohol-dependents often express distinct impairments in visual processing abilities, whereas the verbal functions are relatively preserved (Fabian *et al.* 1994; Wegner *et al.* 2001; Stavro *et al.* 2013). In particular, abstract reasoning, visuospatial and problem solving abilities seem to be frequently impaired, whereas linguistic functions, namely, phonological processing (related to speech sounds), orthographic processing (related to visual structure of written words) and semantic processing (related to meaning of linguistic tokens) are relatively preserved after years of heavy alcohol consumption (Crews *et al.* 2005 ; Chanraud *et al.* 2009). These linguistic functions have classically been associated with parietal and temporal lobes (Mummery *et al.* 1999; Gilman *et al.* 2010). Numerous neuroimaging studies have shown diffuse cortical atrophy in alcohol-dependent subjects in fronto-parietal lobes (Chanraud *et al.* 2007), the medial temporal lobe and cingulate gyrus

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(Sullivan 2003; Sullivan *et al.* 2003; Demirakca *et al.* 2011). Furthermore, these are the areas known to get activated during a wide range of language tasks in healthy subjects (Malogiannis *et al.* 2003; Pallier *et al.* 2003; Seghier *et al.* 2004; Chanraud *et al.* 2009). Despite the fact that language processing areas show reduced gray and white matter volumes, the linguistic functions are relatively preserved. Therefore, the underlying neural correlates for preserved linguistic functions need further exploration.

Studies have shown that alcohol-dependent subjects either set up some compensatory mechanisms or activate a different neural system compared to control subjects for equivalent performance during various cognitive tasks like working memory, attention, simple decision making, etc. (Pfefferbaum *et al.* 2001; Gilman *et al.* 2010; Campanella *et al.* 2013). However, the previous studies mainly focused on identifying underlying neural mechanisms associated with impaired cognitive skills in alcohol-dependents. To the best of our knowledge only one study has investigated the preserved language skills despite mild to severe cortical atrophy in language processing areas in alcohol-dependents (Chanraud *et al.* 2009). The authors have shown that alcohol-dependent subjects exhibited greater fMRI response in left middle frontal gyrus, right superior frontal gyrus and cerebellar vermis as compared to controls while performing an auditory language task despite comparable task performance. Taking this into account, we aimed to further explore the preserved language skills in alcohol-dependent subjects considering a lexical semantic component of language domain. Lexico-semantic processing (word processing) subserves many important cognitive functions making it ideally suited for exploration of language circuitry (Binder *et al.* 1996, 1997).

Like any cognitive task, lexical semantic processing is neurally underpinned not by a single area but a set of areas functioning as a large-scale cortical network involving fronto-temporal regions (Elizabeth *et al.* 2009; Matthew *et al.* 2010), parietal lobule (Grossman *et al.* 1997), angular gyrus, supra marginal gyrus (Geschwind 1965) and inferior prefrontal cortex (Chee *et al.* 2001; Marinkovic *et al.* 2003). As lexical semantic judgment is a complex task that requires numerous cognitive operations such as working memory, attention, visuospatial processing, inhibitory control and decision making, a matching baseline in fMRI task paradigm was designed to require similar processing in terms of visual encoding, decision process and motor response execution, without the need for semantic judgment.

The main aim of this present study was to investigate the functional correlates of preserved language processing in alcohol-dependent subjects. To that end, we used fMRI to scan alcohol-dependent subjects and healthy controls during a lexical semantic judgment based task. Based on previous neuropsychological and fMRI studies, we hypothesized that the preserved language skills in alcohol-dependents would either be associated with compensatory brain responses in parieto-temporal brain regions or recruitment of some different neural networks for a visual language processing task.

2. Methods

2.1 *Participants*

Two groups of subjects were investigated in the study: Alcohol-dependents and Normal healthy controls (see table 1 for details).

2.1.1 *Alcohol-dependent subjects:* The study included 18 male alcoholic patients (mean age 36.55±5.06 (SD) years). In total we reported here the results of only 16 patients, since we had to exclude 2 patients due to head motion exceeding ±1.5 mm. At the time of study, patients had abstained from alcohol during in-patient detoxification treatment program at Department of Psychiatry, Base Hospital, Delhi, India, for 17.5±4.5 days (range 14–30 days) as verified by random administration of alcohol breath test and gamma glutamyl transferase (GGT) levels. The GGT test is widely used as a marker for alcohol intake, with elevated levels of GGT indicating excessive alcohol consumption. Years of education were 10±1.89 (SD) years. All participants were right-handed as self-reported. All patients were diagnosed as alcohol-dependent according to DSM-IV criteria and had no other psychiatric axis I disorders, no past history of dependency or current abuse of other drugs as verified by random urine drug testing and Structured Clinical Interview for DSM IV (SCID) (First *et al.* 2007), performed by the hospital team. Imaging studies were carried out at Institute of Nuclear Medicine and Allied Sciences (INMAS), Lucknow Road, Timarpur, Delhi, India. Inclusion criteria for alcohol-dependence patients comprised the following: (i) less than three withdrawal periods as more than two experiences of withdrawal may be associated with greater cognitive impairment in alcoholic subjects (Duka *et al.* 2003), (ii) detoxification for at least 2 weeks (abstinence assessed by biological norms, normalized levels of GGT, and (iii) no lorazepam or sedative medication for at least 7 days. All the alcoholic patients were otherwise clinically normal. The clinical assessment included detailed medical history, neurological and neuropsychological examinations, and laboratory tests.

2.1.2 *Controls:* The control group was recruited from INMAS, Delhi. This group was composed of 18 healthy male individuals (mean age 35.25±3.79 (SD) years), with no past history of alcohol dependence and any other type of drug abuse .The controls were matched with the alcoholics for age, sex, handedness and years of education were 10±1.85 (SD) years.

For all subjects, the exclusion criteria were illness (medical, neurological or psychiatric), history of head injury with loss of consciousness, stroke, presence of metallic

Table 1. Mean and SD of demographic and neuropsychological data for each group

Characteristics	Alcohol-dependent subjects (n=16) Mean±SD	Controls (n=18) Mean±SD
Age (years)	36.55 ±5.06	35.25 ±3.79
DRS score (verbal IQ)	1.25 ±0.21	1.15 ±0.7
MMSE score	28.5 ±1.22	29.5 ±1.67
Education(yr)	10 ±1.89	10 ±1.85
Amount of alcohol consumption[a]	153.3 ±27.3	——
Alcohol consumption (per day during the 3 months preceding detoxification)[a]	240± 21.8	——
Duration of alcohol dependence	3.43 ±1.3	——
Age at first drinking	23.7 ±3.1	——
Abstinence (days)	17.5 ±4.5	——
Handedness (Right/left)	16/0	18/0

[a] Consumption was defined as grams of pure alcohol/day.

implants or body tattoos, orthodontic appliances, anxiety, pervasive developmental disorders or depressive disorders or other major brain abnormalities on MRI scans. The local ethics committee approved the study and written informed consent was obtained from all participants after the procedures had been fully explained.

2.2 *Language profile information*

All the participants received an extensive background language assessment and a comprehensive language-use questionnaire (Marian *et al.* 2007; Das *et al.* 2011). In the questionnaire, participants answered questions regarding place of residence for longest period, first language, second language and their ages of acquisition, years of education in first language(Hindi for all subjects) and in second language (English for all subjects) and hours spent reading one/both languages. In self language assessment, the participants rated themselves on a scale of 0–10 on their conversation, reading and writing skills. Both the questionnaires are present in supplementary table 2.

2.3 *Neuropsychological testing*

All participants underwent the Mini Mental State Examination (Folstein *et al.* 1975) and a battery of neuropsychological tests (PGIBBD) on the day of the MRI acquisition or within the subsequent 3 days (Chanraud *et al.* 2007). The original version of MMSE was administered by a psychologist to all the subjects. PGI battery of brain dysfunction (PGIBBD) was developed at PGIMER, Chandigarh, India (Pershad and Verma 1990; Sahu *et al.* 2005). The battery is administered in Hindi, the first language of most subjects, and has been developed and validated for use in the Hindi-speaking population. The battery consists of five major tests: Memory scale (Wig *et al.* 1983), Performance scale, Verbal adult intelligence scale, Bender gestalt test and Nahor Benson test (Nahor and Benson 1970), which assesses a wide variety of cognitive abilities. The deficits were reported as DRS (dysfunction rating score). We selected Verbal adult intelligence scale tests from this test battery, in which alcohol-dependent subjects are known to perform at equivalent levels as compared to healthy subjects. Dysfunction scores of 0 shows no dysfunction in any domain. Scores of above 0 are in the direction of impairment.

2.4 *Semantic judgment task*

The semantic judgment task was conducted in English language. It was divided into two conditions: Semantic judgment (Active) and matching control (Baseline). In the active condition, abstract and concrete words were randomly presented and the subjects had to choose whether the words were concrete or abstract, whereas in the baseline condition, subjects had to choose whether the words were uppercase or lowercase, which were also presented randomly. The stimulus words (abstract and concrete, non-words) were selected from previously used word lists (Gabrieli *et al.* 1996; Poldrack *et al.* 1999). Word frequency and word length did not differ significantly between these lists (P-value ≤ 0.2). Across these word lists, mean word frequency was 63.4 for abstract words and 47.0 for concrete words. The word list used for the study is presented in supplementary table 1. Non-words used in experiment were chosen from a set of pronounceable words created by

changing one consonant in a set of medium frequency English words (Poldrack *et al.* 1999); these non-words are also present in supplementary table 1.

2.5 *Preparation and positioning*

All subjects were first introduced to the task and response device in out-of-magnet training that included introduction and instruction slides as well as sample trials of semantic judgment and Control trials on a laptop to make sure that they understood the task. Training was geared at thoroughly familiarizing participants with the modes of stimulus presentation, task requirements and response options.

2.6 *MRI acquisition*

The participants were scanned inside a 3 T whole-body MRI system (Magnetom Skyra, Siemens, Germany) equipped with a circularly polarized 20-channel matrix head and neck coil and 45 mT/m actively shielded gradient system. Subjects lay in the supine position with their heads supported and immobilized within the head coil using foam-pads (vendor provided), to minimize head movement and gradient noise. Thirty-six axial slices parallel to the bicommissural plane through the fronto-parietal cortex covering the whole brain volume using gradient echo-based interleaved EPI sequence (matrix = 64×64, field of view = 210 mm, TE = 36 ms, TR = 3 s, flip angle = 90°, slice thickness = 3 mm, voxel size = 3.28×3.28×3 mm^3) were obtained. For anatomical reference, a T_1-weighted 3D gradient echo sequence (MPRAGE: Magnetization Prepared Rapid Acquisition Gradient Echo, 160 sagittal slices, slice thickness = 1 mm, field of view = 256 mm, TR = 1900 ms, TE = 2.07 ms) image data set was acquired coplanar with the functional scan, to allow for spatial registration of each subject's data into a standard coordinate space.

2.7 *fMRI protocol*

Block paradigm (BABABABA….) with alternating phases of activation (A) and baseline (B) was chosen. 182 sequential image volumes (belonging to six cycles + one baseline for eliminating T_1 saturation effects and acclimatization of the patient to the gradient noise) were taken. The activation phase (42 s duration) involved a semantic judgment task involving a total of 78 stimuli (13 stimuli per active phase) in which subjects had to judge whether the words were abstract or concrete, while the baseline phase (42 s duration) involved a matching control task in which non-words were presented and the subjects had to judge whether the words were in uppercase or in lowercase. The total fMRI acquisition time was 9 min and 6 s including the activation and baseline phase. Each stimulus was shown for 1.5 s with an interstimulus interval of 1.5 s. During each phase, an instruction slide was displayed for 3 s before the stimuli presentation to remind patients about the upcoming task. For active phase, the instruction slide read '*Whether abstract or concrete??*' and for baseline phase, the instruction slide read '*Whether uppercase or lowercase??*'.

Stimuli were presented using fMRI hardware from NordicNeuroLab and the subject's response was monitored with the help of Nordic response device system (Nordic neuro lab (*http://www.nordicneurolab.com/ProductsandSolutions/NordicfMRIsolution/index.aspx*). The timing and switching of visual stimuli were automatically controlled by TTL signals incorporated in the pulse-timing program. Timing of stimuli presentation was synchronized with the scanner image volume acquisition rate. Response times (RT) and response accuracies (RA) were recorded and stored on a PC outside the MR scanner room, for off-line statistical analysis.

2.8 *Data analysis*

At first, fMRI data were transformed into NIFTI format. fMRI image data were processed with Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK, *http://www.fil.ion.ucl.ac.uk/spm*) software package implemented in MATLAB R2008a (Version 7.6.0, Math works, Sherbon, MA). The first 14 brain volumes (one baseline phase) of each fMRI data set were discarded to remove the initial transit signal fluctuations and subsequent images were re-aligned within the session to remove any minor head movements. Translational or rotational movement of greater than 1.5 mm was not considered for analysis. The T1-weighted high-resolution anatomical images were co-registered with fMRI images and spatially normalized according to the Montreal Neurological Institute (MNI) brain template. The time-course images were normalized using the same normalization parameters and then smoothed with a 6×6×6 mm^3 (full width at half maximum) Gaussian smoothing kernel. The EPI images were high-pass-filtered (128 s) to remove artifacts due to cardio respiratory and other cyclical influences. A statistic parametric map (SPM) was generated for each subject under each condition by fitting the stimulation paradigm to the functional data, convolved with a hemodynamic response function. Condition-specific effects at each voxel were estimated using the general linear model (Friston and Worksley 1995). Individual first-level contrast images were generated for the semantic judgment task versus baseline contrast (FWE corrected, $P<0.05$). One-sample *t*-test in both the groups was performed to generate

Table 2. Language profile information for both the groups

Language background questionnaire	Alcohol dependents (n=16) Mean±SD	Controls (n=18) Mean±SD	*p*-Value
Years of education	10.05±1.99	10.03±1.98	0.51
First language (Hindi/English)	16/0	18/0	
Second language (Hindi/English)	0/16	0/18	
Age of acquisition of first language	3.17±0.81	3.12 ±0.53	0.85
Age of acquisition of second language	5.74±0.98	5.71±0.21	0.62
Self-assessment questionnaire			
Proficiency in English (scale of 0-10)			
Conversation	5.11±0.21	5.24±0.11	0.42
Reading	6.91±0.34	6.72±0.41	0.37
Writing	6.36±0.28	6.41±0.13	0.83
Reading habit (hours spent/day)	2.1±0.64	2.2±0.31	0.72

an average activation map using the contrast images from the single-subject analyses. For the between-group analyses, two-sample *t*-test was performed. Since age, duration of alcohol dependence, DRS and response time might influence the BOLD activation pattern in the two groups, they were added as covariates of no interest in the two-sample *t*-test. The resulting statistical map was set at a combined threshold of $P<0.001$ for each voxel and a minimum cluster size > 75 voxels for one sample *t*-test and >11 voxels for two sample *t*-test, which resulted in a corrected threshold of $P<0.05$ as determined by AlphaSim in REST software (*www.restfmri.net*<*http://www.restfmri.net*), as no cluster survived on applying FWE correction. This approach of combining voxel probability threshold with a nonarbitrary minimum cluster size threshold protects against false-positives (Type 1 error) based on the assumption that meaningful activation in fMRI is spatially clustered (Forman *et al.* 1995). For a given voxel-level threshold, the required minimum cluster size for both within and between group analysis was determined by Alphasim via Monte Carlo simulation.

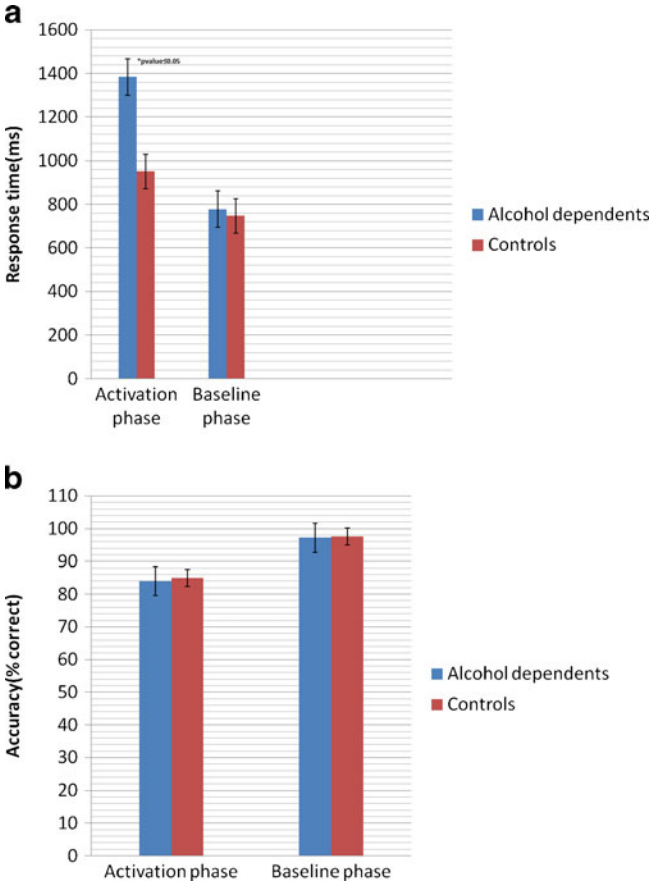


Figure 1. Behavioural data indicating (**a**) response times and (**b**) accuracy.

The anatomical representation of the clusters was related to cytoarchitechtonic maps as implemented in SPM Anatomy Toolbox (Eickhoff *et al.* 2005). The toolbox provides a routine, standardized application of probabilistic cytoarchitectonic maps as an anatomical reference for functional activations. It includes the functionality for the construction of summary maps combining probability of several cortical areas by finding the most probable assignment of each activated voxel to one of these areas.

BOLD contrast estimates were also extracted from the 8 mm ROIs defined on the regions showing group differences in two-sample *t*-test using MarsBaR toolbox of SPM (*http://marsbar.sourceforge.net/*).

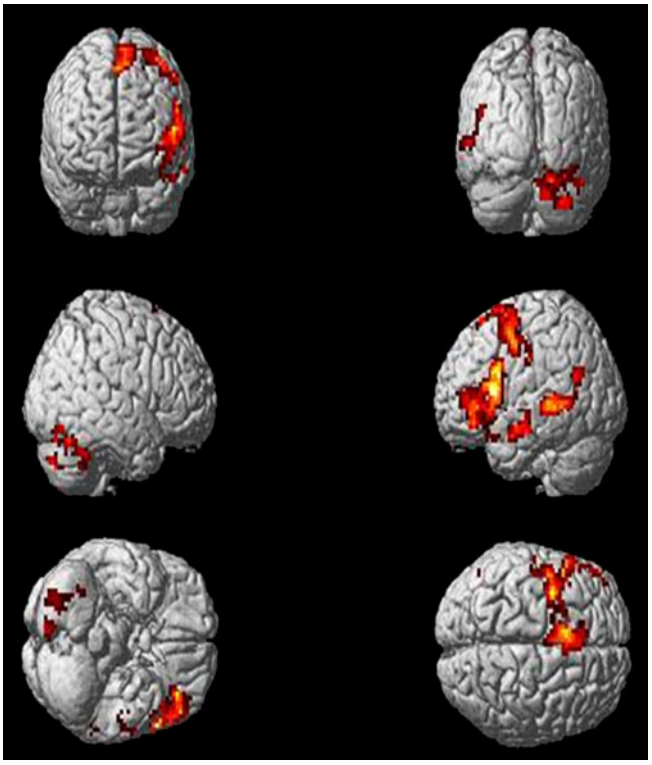


Figure 2. Three-dimensional rendered whole brain activation map for alcohol-dependent subjects. Activation maps are displayed at a threshold of $t > 10$, $p < 0.001$ for magnitude, $p < 0.05$, alphasim corrected.

3. Results

Based on the information provided by participants in the language questionnaire, it was seen that for all the participants the first language was Hindi and the second language was English. All the participants were equally proficient in English as self-reported (see table 2 for details).

3.1 *Behavioural performance*

During the active phase (semantic judgment trials), there was no difference with respect to accuracy (two sample *t*-test, $P \leq 0.12$) between alcohol-dependent subjects (percentage accuracy: mean = 84.0%, SD = 4.34; total no. of responses: mean = 77.5, SD = 0.31; no. of correct responses: mean = 65.5, SD = 0.42) and controls (percentage accuracy: mean = 84.90%, SD = 2.67; total no. of responses: mean = 77.5, SD = 0.21; no. of correct responses: mean=66.3, SD = 0.34). However, there was a significant difference in the response times (two sample *t*-test, $P \leq 0.01$) of the two groups. Control subjects (mean=951 ms, SD=83.29) performed significantly faster than alcohol-dependent subjects (mean=1384 ms, SD=78.31).

During the baseline phase (Case judgment trials), there was no difference between alcohol-dependent subjects (mean = 97.2%, SD = 3.35) and controls (mean = 97.6%, SD = 2.28) with respect to accuracy. Also, the response times for alcohol-dependent subjects (mean = 778 ms, SD = 84.12) and controls (mean = 747 ms, SD = 78.42) did not differ significantly between the two groups (two sample *t*-test, $P \leq 0.85$) (figure 1).

Additionally, the subjects processed the abstract and concrete words equivalently. The mean response times for abstract word processing (alcoholics = 1.96 ms, SD = 0.46; controls = 0.99 ms, SD = 0.25) and concrete word processing (alcoholics = 1.51 ms, SD = 0.44; controls = 0.906 ms, SD = 0.15) did not differ significantly between the two groups (two sample *t*-test, $P \leq 0.9$). Also, there were no differences with respect to response accuracy for abstract

Table 3. Regions of significant activity observed in alcohol dependent subjects during the lexical semantic judgment task

Activation size (Voxels)	T-value	MNI coordinates (X,Y,Z)			Area
658	16.75	−45	11	22	LIFG
	12.16	−45	11	31	LMFG
508	10.29	−48	−4	46	LSMA
	5.23	−51	−19	37	LSMG
403	8.54	21	−73	−23	Right cerebellum
297	8.92	−57	−40	−2	LMTG
113	6.09	−6	−46	4	Left CG
	6.04	−12	−31	−5	Left LG
105	8.45	−48	−1	−20	MTG

Peaks of activation at *p*-value≤ 0.001 (uncorrected) threshold. Alphasim corrected (parameters: *p*-value ≤0.05, voxels=75). IFG=inferior frontal gyrus, MFG=middle frontal gyrus, SMA=somatosensory motor area, MTG=middle temporal gyrus, CG-Calcarine gyrus, LG= Lingual gyrus.

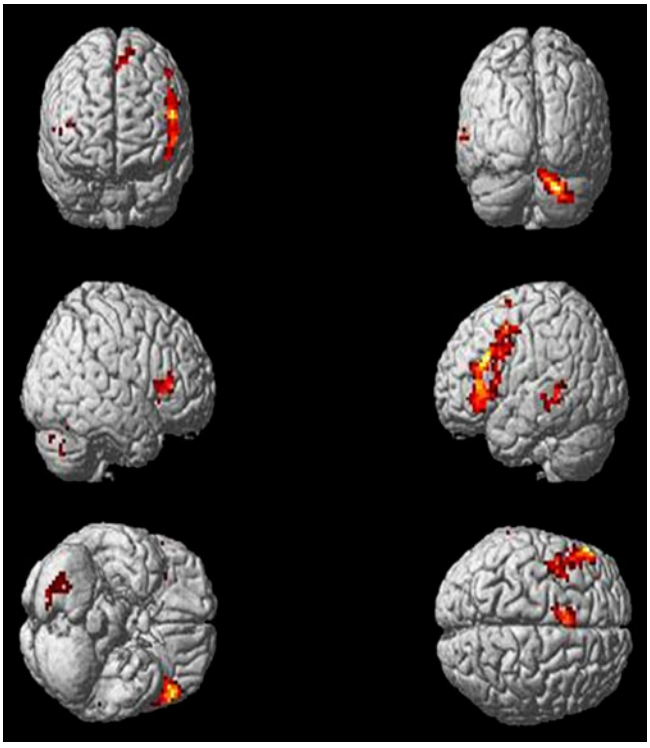


Figure 3. Three-dimensional rendered whole brain activation map for control subjects. Significant clusters are superimposed on the anatomical render (SPM8). Activation maps are displayed at a threshold of t >10, $p < 0.001$ for magnitude, $p < 0.05$, alphasim corrected.

(alcoholics = 82.79%, SD = 0.68; controls = 84.46%, SD = 0.89) and concrete words (alcoholics = 84.42%, SD = 0.96), controls = 84.89%, SD = 1.2) in both the groups.

3.2 *fMRI*

3.2.1 *Within-group analysis*

- Alcoholic group: Left-sided activation was seen in the inferior frontal gyrus (IFG), middle frontal gyrus (MFG), supramarginal gyrus (SMG), somatosensory motor area (SMA), middle temporal gyrus (MTG), Calcarine gyrus (CG) and lingual gyrus (LG). Right-sided activation was observed in the cerebellum (see figure 2 and table 3 for details).
- Control group: Bilateral activation was seen in the inferior frontal gyrus (IFG). Left-sided activation was seen in middle temporal gyrus (MTG) and somato sensory motor area (SMA). Right-sided activation was seen in the cerebellum (see figure 3 and table 4 for details).

3.2.2 *Between-group analysis*

- Controls > alcohol-dependents: When subtracting the alcoholic group from the control group, there remained no significant areas showing greater activation.
- Alcohol-dependents > Controls: When subtracting the control group from alcoholic group, there remained activation in left supramarginal gyrus (SMG), right precuneus (RP), left precuneus (LP), left angular gyrus (LAG) and left middle temporal gyrus (LMTG) (see figure 4 and table 5 for details).

3.3 *ROI analysis*

The contrast estimates of BOLD response as obtained using MarsBaR toolbox in the regions obtained in two-sample t-test were significantly higher in alcohol-dependent subjects as compared to controls (see figure 5 for details).

4. Discussion

The present preliminary study was designed to look for the neural recruitment pattern attributed to preserved lexico-semantic processing in alcohol-dependent subjects using fMRI. Behavioural results showed that there were no significant differences in the response accuracy between the two subject groups, but response times were significantly

Table 4. Regions of significant activity observed in control subjects during the lexical semantic judgment task

Activation size (Voxels)	T-value	MNI coordinates (X,Y,Z)			Area
433	11.43	−39	8	25	LIFG
199	16.32	21	−79	−32	Right cerebellum
95	8.73	48	29	7	RIFG
78	9.21	−51	−31	−8	LMTG
76	10.14	−12	2	64	SMA

Peaks of activation at p-value≤ 0.001 (uncorrected) threshold. Alphasim corrected (parameters: p-value ≤0.05, voxels=75). IFG= Inferior frontal gyrus, MTG= Middle temporal gyrus, SMA= somatosensory motor area.

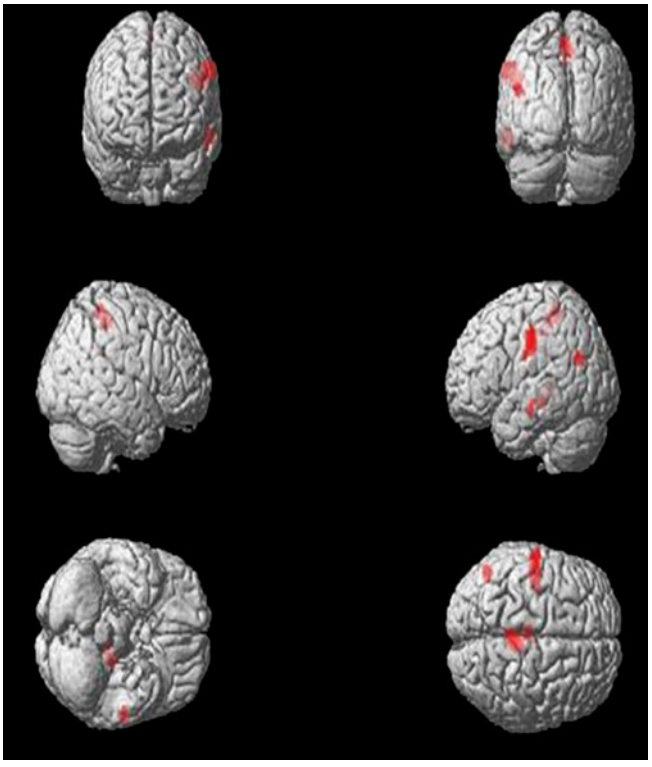


Figure 4. Three-dimensional rendered whole brain activation map for regions that responded more strongly in alcoholics as compared to controls. Activation maps are displayed at a threshold of $t > 5$, $p < 0.001$ for magnitude, $p < 0.05$, alphasim corrected.

different, with alcohol-dependents taking more time than controls for performing the task. The increased response times could be interpreted as reflecting increased task demands in alcohol-dependents for maintaining an equivalent performance.

Table 5. Results for the whole brain analysis for alcohol dependents/controls contrast

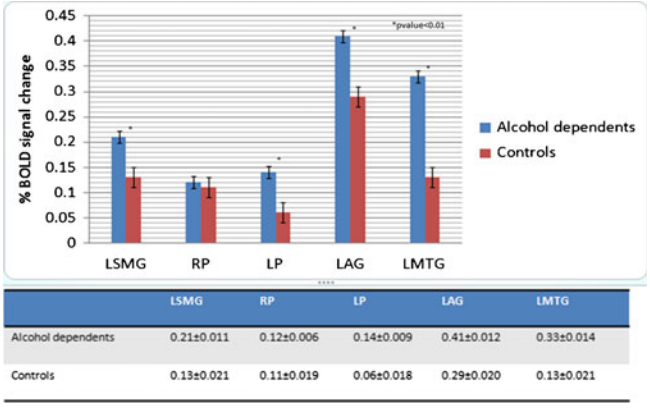
Cluster size	T-value	MNI coordinates			Structure
		X	Y	Z	
95	4.75	−45	−16	28	LSMG
23	4.24	−57	−14	−12	LMTG
14	4.05	3	−44	60	RP
14	4.72	−21	−52	43	LP
13	4.47	−57	−4	13	LAG

Peaks of activation at p-value≤ 0.001 (uncorrected) threshold. Alphasim corrected (parameters: p-value ≤0.05, voxels=11). LSMG=left supramarginal gyrus, LMTG=left middle temporal gyrus, RP=right precuneus, LP=left precuneus, LAG=left angular gyrus.

In our study, the control group showed activation patterns consistent with those reported in literature on the network of brain regions critically involved in language processing (Grossman *et al.* 1997; Malogiannis *et al.* 2003; Pallier *et al.* 2003; Seghier *et al.* 2004; Andoh *et al.* 2006, 2007; Chanraud *et al.* 2009). A considerable part of this same network was activated by alcoholic group as well, specifically frontal gyrus, temporal gyrus, precuneus, cingulate cortex and cerebellum. On direct comparison of the two groups, alcohol-dependent subjects showed enhanced activation in parietal lobe (precuneus bilaterally, left angular gyrus and left postcentral gyrus) and left temporal lobe regions as compared to controls.

Left temporal gyrus had been demonstrated to be involved in lexico-semantic processing in healthy subjects as evident by various neuroimaging studies (Cappa *et al.* 1981; Damasio *et al.* 1996; Chertkow *et al.* 1997; Mummery *et al.* 1999; Pallier *et al.* 2003; Andoh *et al.* 2006; Das *et al.* 2011). It is also referred to as basal temporal language area (Burnstine *et al.* 1990), having direct connections to wernicke's area (Di Virgilio and Clarke 1997), which is considered to be the site for semantic processing of language as per classical language area hypothesis. This region has also been proposed to play a role in allowing the semantic system access to stored lexical information (Foundas *et al.* 1998). The greater activity in the left middle temporal gyrus might reflect increased task demands in alcoholic subjects for storage and retrieval of semantic knowledge critical for semantic judgment.

Parietal lobe was earlier considered to play an important role in the manipulation of spatial information (Prabhakaran *et al.* 1997; Kroger *et al.* 2002; Lee *et al.* 2006), or visual inspection and attention (Christoff *et al.* 2001). However, recent imaging studies have shown the role of parietal lobe



	LSMG	RP	LP	LAG	LMTG
Alcohol dependents	0.21±0.011	0.12±0.006	0.14±0.009	0.41±0.012	0.33±0.014
Controls	0.13±0.021	0.11±0.019	0.06±0.018	0.29±0.020	0.13±0.021

Figure 5. Beta estimates (% BOLD signal change) in alcohol-dependents>control contrast. LSMG=left supramarginal gyrus, RP= right precuneus, LP= left precuneus , LAG= left angular gyrus, LMTG= left middle temporal gyrus.

in language processing and semantic memory encoding and retrieval (Buckner *et al.* 2005; Lundstrom *et al.* 2005; Klostermann *et al.* 2008). The angular gyrus (AG) and the supramarginal gyrus (SMG) are the brain regions in the parietal lobe associated with complex language functions (i.e. reading, writing and interpretation of what is written). The SMG seems to be involved in phonological and articulatory processing of words, whereas the AG seems more involved in semantic processing (Warrington and Shallice 1979; Demonet *et al.* 1992; Price and Friston 1997). Additionally, SMG and AG also help the brain to classify and label things, which is a prerequisite for forming concepts and thinking abstractly. Together, AG and SMG constitute a multimodal associative area that receives auditory, visual and somatosensory inputs. The neurons in this area are thus very well positioned to process the phonological and semantic aspect of language that enables us to identify and categorize objects. Brain imaging studies have shown that SMG and AG are connected by large bundles of nerve fibres to both broca's area and wernicke's area (Catani and Ffytche 2005), which are centres of language processing in healthy subjects. Information might therefore travel between these last two areas either directly, via the arcuate fasciculus, or by a second, parallel route that passes through theses parietal lobe regions. The task-related greater activity in these areas in alcohol-dependents as compared to controls might suggest a compensatory mechanism for efficient interpretation of word meanings, concept formation and word categorization.

Additionally, greater activation was also observed bilaterally in precuneus in alcohol-dependent subjects as compared to controls. Studies have shown the role of precuneus in mental imagery and conscious information retrieval processes in healthy subjects (Bitan *et al.* 2005; Lundstrom *et al.* 2005; Vogt and Laureys 2005; Kim *et al.* 2011). The greater activation in precuneus suggests the difficulty in retrieval of stored mental images related to the presented words rather than the formation of new mental imagery as suggested by various earlier studies (Kosslyn *et al.* 1993; Kiyosawa *et al.* 1996).

Our findings are in line with previous studies suggesting compensatory mechanisms in alcohol-dependents for various cognitive tasks (Gilman *et al.* 2010; Campanella *et al.* 2013). In a study by Campanella *et al.* (2013), higher bilateral activity was observed in the pre-supplementary motor area during a working memory task in binge drinkers than matched controls, which was suggestive of possible compensatory cerebral changes in them that facilitated normal behavioural performance. In another study by Gilman *et al.* (2010), significantly increased activation in frontal, limbic, and temporal regions was observed in alcohol-dependent subjects relative to the controls reflecting a compensatory recruitment of brain regions to perform simple decision-making tasks. Similarly, in our study the enhanced activation observed in alcohol-dependents as compared to controls could reflect an inefficient processing of the brain or a compensatory mechanism for altered brain anatomy in parieto-temporal brain regions generally observed in alcohol dependants, such that a large number of neurons have to be activated in order to meet the task demands. However, functional connectivity analysis using Dynamic Causal Modelling (DCM) on the existing data might shed further light on the differences in the involved neural mechanisms for task performance among the two groups.

A possible limitation of the study was that the interpretations were drawn from a sample of men. As alcohol-related neuropsychological deficits and brain alterations are gender dependent, the questions raised in this study still remain for alcoholic women.

5. Conclusion

Ours is one of the few published fMRI studies on preserved language processing abilities in alcohol-dependents. Also, to the best of our knowledge, this is the first report on preserved lexical semantic judgment ability observed in them. We found that alcohol-dependent subjects showed enhanced neural activation as compared to controls while performing a lexical semantic judgment task despite similar behavioural performance. However, on direct comparison of the two groups, the results did not survive correction for multiple comparisons; therefore, the present findings reflect a trend towards setting up of a compensatory mechanism, particularly in the parieto-temporal circuits in alcohol-dependents, that might be due to a decreased efficiency of relevant brain networks, at neural and cognitive levels. The study, thus contribute to the limited available literature on physiological mechanisms underlying preserved language skills in alcohol-dependents.

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